Rates of Selected Birth Defects in Relation to Folic Acid Fortification, Hawaii, 1986-2002

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Abstract

Because of studies suggesting that folic acid use reduces risk of various birth defects, the Unites States fortified enriched cereal grains with folic acid in 1998. To determine whether this fortification reduced rates for birth defects in Hawaii, rates were calculated before and after fortification. Of the 19 birth defects categories studied, the rates for 16 were lower after fortification.

Introduction

Investigations over the last several decades have found that periconceptional use of folic acid by women reduces risk of neural tube defects (NTDs), particularly anencephaly and spina bifida, among their offspring.[1,2] As a result, researchers have attempted to determine whether there were similar associations between folic acid or multivitamin use and other birth defects. Studies have reported that folic acid or multivitamin use reduced the risk of anotia/microtia, conotruncal heart defects, ventricular septal defect (VSD), atrial septal defect (ASD), coarctation of aorta, oral facial cleft (cleft lip, cleft palate), pyloric stenosis, imperforate anus, urinary tract anomalies, limb reduction deformities, omphalocele, and trisomy 21.[2-7] However, in many of these studies the reduction in risk was not as great as that found for NTD, the reduction was not statistically significant, and/or the relationship between folic acid and risk of the birth defects varied between studies, with some finding no reduction in risk.

In an effort to reduce the number of NTD-affected pregnancies in the United States, in 1996 the Food and Drug Administration required that all enriched cereal grains (flour, corn meal, paste, and rice) in the country must be fortified with folic acid by January 1, 1998.[8] In order to determine the effectiveness of this policy, various investigations have compared the rates of selected birth defects in the United States before and after fortification using data from population-based birth defects registries. Several studies found significantly lower rates for NTDs, particularly spina bifida, after fortification, although any observed declines in anencephaly rates were frequently not statistically significant.[9-13] Studies of the potential impact of folic acid fortification on the rates of other birth defects either did not observe any decline in rates after fortification or the decline was not statistically significant.[10,14-17]

However, there are limitations to many of these investigations. One investigation used birth certificates to identify cases.[13] But birth defects are not reliably recorded on birth certificates, and a portion of fetuses with birth defects do not result in live births but either expire in utero or are prenatally diagnosed and electively terminated.[18,19] In one study,[12] the data was collected via "rapid ascertainment", where NTD cases were to be identified and reported as soon as possible and not to wait to use the standard operational procedures of the registries. It is possible that the reporting cases through rapid ascertainment may be incomplete. A number of the studies compared only brief time periods of several years before and after fortification.[9,11-14] However, birth defects rates can vary wildly from year to year; thus the ratio of rate before and after fortification could depend on the time periods chosen.[13]

Some investigations included data from birth defects registries in multiple states.[9,12] Although this resulted in large data sets and reduced the impact of wide variations in birth defects rates among small populations, the birth defects registries varied in their operations, e.g., ascertainment methodologies and inclusion criteria [20] and some of the registries have changed their operations over the years. For instance, registries may have changed the geographic area covered from one year to the next.[14,20] Moreover, by examining rates at the national level, regional and state-specific differences were obscured.

The objective of the present investigation was to examine the potential impact of folic acid fortification on the rates of selected birth defects using data from a population-based birth defects registry in Hawaii not subject to many of the limitations outlined above. Although the authors have performed similar analyses for several birth defects previously,[15-17] this analysis includes additional years of data.

Methods

Data were compiled from the Hawaii Birth Defects Program (HBDP), an active statewide population-based birth defects registry.[20] The registry includes infants and fetuses of any pregnancy outcome (live birth, fetal death, elective termination) of any gestational age where the pregnancy ended in Hawaii and one or more reportable birth defects were identified between conception and one year after delivery. Thus the HBDP includes fetuses where the birth defect was prenatally diagnosed and the fetus was electively terminated. Trained HBDP staff ascertain eligible infants and fetuses and collect demographic and clinical information through review of logs and medical records at all delivery hospitals, tertiary care pediatric facilities, institutions that perform elective terminations secondary to fetal defects, genetic counseling centers, and cytogenetic laboratories and all but one of the major prenatal ultrasound facilities in the state. Because of this multiple source system, the ascertainment of infants and fetuses with diagnosed birth defects is believed to be as complete as possible. Also, any changes the HBDP have made in ascertainment practices over the years, e.g., inclusion of early elective terminations, were all instituted retrospectively.

Cases were all infants and fetuses with one or more of 19 selected birth defects categories delivered during 1986-1996 or 1999-2002. Instances where the diagnosis was listed as "possible" or "probable" were excluded from the analysis. The particular birth defects were chosen because previous studies had reported maternal folic acid or multivitamin use reduced risk of the defects. Cases with more than one of these selected birth defects were included in all relevant birth defects categories with the exception of cases with both anencephaly and spina bifida that were classified only as anencephaly.

The cases were sorted into two sets of time periods based on folic acid fortification status. The first set was 1986-1996 (pre-fortification) and 1999-2002 (mandatory fortification). This set of time periods is longer that those reported in the other studies and thus less likely to be subject to wide variations in rates during one or several years. The second set was 1993-1996 (pre-fortification) and 1999-2002 (mandatory fortification), thus using equal lengths of time both before and after fortification. No attempt was made to adjust the delivery years for fetal deaths and elective terminations should the pregnancies have gone to term. No adjustments were made for changes in demographic composition of the population between the time periods. The rates for each birth defect were calculated for each time period using denominators derived from birth certificates. The rates during mandatory fortification were then compared to the corresponding pre-fortification rate by calculating rate ratios and 95 percent confidence intervals (CIs) using Poisson probability.

Results

Table 1 compares the rates for selected birth defects during 1986-1996 (pre-fortification) and 1999-2002 (post-fortification). For all but three of the birth defect categories, the birth defect rate had declined after folic acid fortification by 10-100%. However, the decline was only statistically significant for four of the birth defects (truncus arteriosus, oral clefts, pyloric stenosis, and trisomy 21).

Table 2 shows a similar comparison except that the pre-fortification time period was reduced to 1993-1996. Again, all but three of the birth defects categories demonstrated a decline in rate after folic acid fortification. However, in this instance the reduction in rate was statistically significant for five birth defects (NTDs, spina bifida, truncus arteriosus, oral clefts, and pyloric stenosis).

Discussion

This investigation examined the relationship between folic acid fortification and rates for selected birth defects in Hawaii. This study is free from many of the limitations of previous investigations. It used data collected by a population-based birth defects registry with consistent operations that included prenatally diagnosed and electively terminated cases. Moreover, data was available for eleven years prior to fortification and for four years after fortification; thus allowing for utilization of more stable rates in the comparisons. This information is important on the state level because it studies whether folic acid fortification has had a positive impact within the state. In addition, this information is important nationally because it provides additional data on the impact of folic acid fortification in the United States on a variety of birth defects.

This investigation has several limitations. The relatively small number of cases limits the statistical significance of the analysis. Moreover, the authors did not control for temporal changes in demographic factors such as race/ethnicity or maternal age distribution.

This investigation found NTD rates, and particularly spina bifida rates, to be lower in the time period after folic acid fortification, an observation consistent with other investigations.[9-13] However, the reduction in NTD and spina bifida rates were only statistically significant when the comparison was made using the four years immediately preceding folic acid fortification (1993-1996) and not when the data available for the entire eleven-year period preceding fortification (1986-1996) were used. This was because the rates for NTDs and spina bifida, and incidentally anencephaly, were actually higher in 1993-1996 than in 1986-1992 (table 3).

When selected birth defects other than NTDs were examined, the rates were observed to be lower after

Table 1.— Rates per 10,000 births of selected birth defects in Hawaii before and after folic acid fortification, 1986-2002

Birth defect	1986-1996 (212,258 births)		1999-2002 (69,363 births)			
	No.	Rate	No.	Rate	Ratio[1]	95% CI[2]
Neural tube defects	187	8.81	48	6.92	0.79	0.56-1.08
Anencephaly	82	3.86	22	3.17	0.82	0.49-1.33
Spina bifida	105	4.95	26	3.75	0.76	0.47-1.17
Anotia/microtia	73	3.44	30	4.33	1.26	0.79-1.95
Conotruncal heart defects	188	8.86	52	7.50	0.85	0.61-1.16
Truncus arteriosus	17	0.80	0	0.00	0.00	0.00-0.74
Transposition of great arteries	85	4.00	34	4.90	1.22	0.80-1.84
Tetralogy of Fallot	93	4.38	20	2.88	0.66	0.38-1.08
Ventricular septal defects	911	42.92	262	37.77	0.88	0.76-1.01
Atrial septal defect	426	20.07	174	25.09	1.25	1.04-1.49
Coarctation of aorta	57	2.69	10	1.44	0.54	0.24-1.06
Oral clefts	443	20.87	110	15.86	0.76	0.61-0.94
Cleft palate alone	160	7.54	37	5.33	0.71	0.48-1.02
Cleft lip with or without cleft palate	283	13.33	73	10.52	0.79	0.60-1.02
Pyloric stenosis	196	9.23	41	5.91	0.64	0.45-0.90
Imperforate anus	115	5.42	34	4.90	0.90	0.60-1.34
Limb reduction deformity	99	4.66	24	3.46	0.74	0.45-1.17
Omphalocele	61	2.87	14	2.02	0.70	0.36-1.27
Trisomy 21	337	15.88	85	12.25	0.77	0.60-0.98

[1]Ratio of rate during 1999-2002 to rate during 1986-1996, [2]95% confidence interval, Any cases with more than one birth defect are included in all relevant categories

Table 2.— Rates per 10,000 births of selected birth defects in Hawaii before and after folic acid fortification, 1993-2002

Birth defect	1993-1996 (76,269 births)		1999-2002 (69,363 births)			
	No.	Rate	No.	Rate	Ratio1	95% CI2
Neural tube defects	82	10.75	48	6.92	0.64	0.44-0.93
Anencephaly	33	4.33	22	3.17	0.73	0.41-1.30
Spina bifida	49	6.42	26	3.75	0.58	0.35-0.96
Anotia/microtia	18	2.36	30	4.33	1.83	0.99-3.49
Conotruncal heart defects	67	8.78	52	7.50	0.85	0.58-1.24
Truncus arteriosus	5	0.66	0	0.00	0.00	0.00-1.20
Transposition of great arteries	35	4.59	34	4.90	1.07	0.65-1.76
Tetralogy of Fallot	28	3.67	20	2.88	0.79	0.42-1.45
Ventricular septal defects	316	41.43	262	37.77	0.91	0.77-1.08
Atrial septal defect	130	17.04	174	25.09	1.47	1.17-1.86
Coarctation of aorta	18	2.36	10	1.44	0.61	0.25-1.40
Oral clefts	158	20.72	110	15.86	0.77	0.60-0.98
Cleft palate alone	59	7.74	37	5.33	0.69	0.44-1.06
Cleft lip with or without cleft palate	99	12.98	73	10.52	0.81	0.59-1.11
Pyloric stenosis	71	9.31	41	5.91	0.63	0.42-0.95
Imperforate anus	42	5.51	34	4.90	0.89	0.55-1.43
Limb reduction deformity	31	4.06	24	3.46	0.85	0.48-1.50
Omphalocele	26	3.41	14	2.02	0.59	0.29-1.18
Trisomy 21	116	15.21	85	12.25	0.81	0.60-1.08

[1]Ratio of rate during 1999-2002 to rate during 1993-1996, [2]95% confidence interval, Any cases with more than one birth defect are included in all relevant categories

Table 3.— Rates per 10,000 births of selected birth defects in Hawaii during various time periods, Hawaii

Birth defect	1986-1992	1993-1996	1999-2002
Neural tube defects	7.72	10.75	6.92
Anencephaly	3.60	4.33	3.17
Spina bifida	4.12	6.42	3.75
Anotia/microtia	4.04	2.36	4.33
Conotruncal heart defects	8.90	8.78	7.50
Truncus arteriosus	0.88	0.66	0.00
Transposition of great arteries	3.68	4.59	4.90
Tetralogy of Fallot	4.78	3.67	2.88
Ventricular septal defects	43.75	41.43	37.77
Atrial septal defect	21.77	17.04	25.09
Coarctation of aorta	2.87	2.36	1.44
Oral clefts	20.96	20.72	15.86
Cleft palate alone	7.43	7.74	5.33
Cleft lip with or without cleft palate	13.53	12.98	10.52
Pyloric stenosis	9.19	9.31	5.91
Imperforate anus	5.37	5.51	4.90
Limb reduction deformity	5.00	4.06	3.46
Omphalocele	2.57	3.41	2.02
Trisomy 21	16.25	15.21	12.25

Any cases with more than one birth defect are included in all relevant categories.

folic acid fortification for all of the birth defects except anotia/microtia, transposition of great arteries, and ASD. The reduction in rate was statistically significant for truncus arteriosus, oral clefts, and pyloric stenosis. The reduction in rate for trisomy 21 was also statistically significant when the comparison was made with the 1986-1996 time period but not with the 1993-1996 time period. Although other studies had reported post-fortification reductions in rates for various birth defects other than NTDs, in none of these instances was the reduction statistically significant.[10,14,15,17]

The findings of this study would tend to support the supposition that fortification of enriched cereal grains have reduced the rates of NTDs and other birth defects in the United States. However, there are other potential explanations for the observed reduction in birth defect rates after 1998. One possibility is that ascertainment of the birth defects declined in the latter part of the study period. This is unlikely because the ascertainment methodology of the HBDP remained constant during 1994-2002. Although several changes in ascertainment were made in 1993, most notably the addition of all elective terminations to the inclusion criteria, these changes were implemented retrospectively. Moreover, if the changes in ascertainment were expected to have any impact, it would be to increase the ascertainment of cases, resulting in an increase in the birth defect rate.

Even if ascertainment did not change, it could be that the diagnosis of the birth defects decreased during the latter part of the time period. If a birth defect is not diagnosed, then it cannot be ascertained. Many of these birth defects can be prenatally diagnosed, a portion of which might be expected to result in elective terminations.[15,17,21-23] Thus if there had been an increase in the prenatal diagnosis and elective termination of selected birth defects in the study population, then there would be a decrease in the number of live births with the defects and a corresponding decrease in the live birth rate. However, this study included prenatal diagnosis and elective terminations. Moreover, the elective termination rates for some of these birth defects is relatively low, and many of these birth defects should be obvious on physical examinations.

It could be that the observed lower birth defect rates observed in 1999-2002 could be due at least in part to a decline that started prior to folic acid fortification. Table 3 provides the rates for the various birth defects for three time periods: 1986-1992, 1993-1996, and 1999-2002. Nine of the birth defects categories demonstrated a continuous decline from one time period to another. Finally, the observed changes in birth defects rates could be due to changes in the demographic composition of the population, which was not controlled for in the analysis, or simply due to chance.

Although research had suggested that maternal periconceptional use of folic acid may reduce the risk for all of the birth defects included in this investigation, significant reductions after folic acid fortification were observed for only a portion of the birth defects categories. There are various reasons why significant reductions in rates were not observed for all of the defects. The enriched cereal grains may not have been fortified with sufficient folic acid to prevent many of the birth defects. Alternatively, for years prior to the fortification various public health organizations had recommended that women of childbearing age take folic acid supplements.[24] If a number of such women were already taking folic acid supplements, then fortification might not have had much impact on reducing risk of the birth defects. The decline in the rates for many of these birth defects prior to fortification could possibly be due to such supplementation. Unfortunately, information on folic acid supplementation by women of childbearing age in Hawaii is not readily available.

A further potential explanation for the lack of a substantial reduction in rates could be that publicity of the associations between particular birth defects and folic acid may increase ascertainment or diagnosis of the birth defects.[19] However, as outlined previously, the HBDP ascertainment methodology did not change substantially during the time period. And since many of the birth defects are rather obvious on physical examination, it is unclear how diagnosis of these defects could be enhanced.

An additional finding of this investigation is that the degree of reduction in rate for specific birth defects, and whether the reduction is statistically significant, depended on the pre-fortification time period used. Other researchers may wish to consider this when deciding what time periods to use in their own investigations.

In conclusion, this study found that of 19 birth defects categories examined, almost all demonstrated lower rates after folic acid fortification. This rate reduction was significant for NTDs, spina bifida, truncus arteriosus, oral clefts, pyloric stenosis, and trisomy 21. However, the degree of reduction and whether the reduction was statistically significant depended on the reference time period used.

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